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APPLICATION NO	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO	CONFIRMATION NO
09/913,728	10/23/2001	Toshio Kitamura	084335-0143	3800

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EXAMINER
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ART UNIT	PAPER NUMBER
1647	12

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Please find below and/or attached an Office communication concerning this application or proceeding.

Application No.	Applicant(s)
09/913,728	KITAMURA ET AL.
Examiner	**Art Unit**
Regina M. DeBerry	1647

Office Action Summary

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 December 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12* is/are pending in the application.

4a) Of the above claim(s) *6 and 10-12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5 and 7-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-12* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 9
4)☐ Interview Summary (PTO-413) Paper No(s) _____
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: _____

Status of Application, Amendments and/or Claims

The amendment filed 23 October 2001 (Paper No. 8) has been entered in full.

The information disclosure statement filed 23 May 2002 (Paper No. 9) was received and complies with the provisions of 37 CFR §§1.97 and 1.98. It has been placed in the application file and the information referred to therein has been considered as to the merits.

Applicant's election without traverse of Group I (claims 1-5, 8 and 9) and SEQ ID NO:1 and SEQ ID NO:2 in Paper No. 11 is acknowledged. Upon further consideration, the Examiner has decided to rejoin Group I (claims 1-5, 8 and 9), drawn to polynucleotide, polypeptide, vector, host cell, method of making the protein and method of screening for a compound with Group III (claim 7) drawn to the partial peptide of the protein of claim 4.

Claims 6, 10-12 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected Group, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 11. Claims 1-5, 7-9 are under examination.

Sequence Rules

The specification is not in compliance with 37 CFR 1.821-1.825 of the Sequence Rules and Regulations. When the description of a patent application discusses a sequence listing that is set forth in the "Sequence Listing" in accordance with paragraph (c) of the Sequence Rules and Regulations, reference must be made to the sequence

by use of the assigned identifier (SEQ ID NO:), in the text and claims of the patent application. The specification refers to sequences in Figures 1, 2A, 2B, but does not identify the sequences by their sequence identifiers. Sequences appearing in drawings may be referenced in the drawings themselves or in the corresponding Brief Description thereof. Appropriate correction is required. **Applicant must submit a response to this Office Action and compliance with sequence rules simultaneously.**

Claim Objections

Claims 1, 5 and 8 are objected to because of the following informalities: The instant claims encompass non-elected inventions (SEQ ID Nos) and require amendment to limit to elected invention. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Appropriate correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-5 and 7-9 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.

In addition claims 1, 4 and 8 are directed to non-statutory subject matter. The instant claims as they stand are not limited to isolated and purified polypeptides and/or polynucleotides and encompass the full length naturally occurring product and therefore read on products of nature.

The instant claims are generally drawn to polynucleotide, polynucleotide encoding the polypeptide, partial peptide, vector, host cell and method of producing the polypeptide. The specification states that the polypeptide claimed in the instant application is a novel cytokine receptor-like protein (Delta1) expressed in blood. The polypeptide is homologous to the receptors that belong to the type I cytokine receptor superfamily. The gene was expressed in the heart, lung, liver and spleen of mice as well as in myeloid and lymphoid cell lines. The membrane proximal region of the protein encoded by the gene could replace the proximal region of human EPOR in signal transduction of proliferation and activation of JAK2 (Janus kinase) The receptor protein has regions suspected to be the box1 and box2 domains, which transduce signals into the cell (page 3, lines 1-14 and page 5, lines 15-23). The specification states that the specific gene expression in the tissue/cell and the structural feature of the receptor-like protein suggest that it functions especially in the immune system as a signal transduction molecule (page 3, lines 14-18).

Generally, the art acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases. Karp (1998, Bioinformatics 14:753-754) states that functional annotations are propagated repeatedly from one sequence to the next with no record made of the source of a given annotation,

leading to a potential transitive catastrophe of erroneous annotations. Incorrect functional predictions can result from a number of causes, including: divergence of function within homologous proteins, confusion or omission of functions across multimodular proteins or simply choosing the strongest homolog as the source of attributed function.

The assertion that the instant invention has biological activities similar to known cytokine type-1 receptors cannot be accepted in the absence of supporting evidence, because the relevant literature reports examples of polypeptide families wherein individual members have distinct, and sometimes even opposite, biological activities. For example, Ozaki *et al.* (2002, J. Biol. Chem. 277:29355-29358) establishes that IL-5 (essential for eosinophil expansion) and GM-CSF (acting mainly on granulocytes and macrophages/monocytes) have a distinctive α chain (IL-5α and GM-CSFRα) but they all share a common β chain, β_c. Disruption of β_c in a murine knock-out model does not cause a severe defect within the hematopoietic system, although signaling in response to IL-5 and GM-CSF is disrupted. In addition, IL-6, IL-11, LIF, OSM, CNTF, NNT-1/BSF-3/CLC and CT-1 are seven cytokines that exert multiple actions but all of them share the gp130 signal transducing molecule as a component of their receptors. In addition, polynucleotides are known in the art to encode polypeptides, yet the polypeptides have no known function.

The response of Ba/F3 cells against IL-3 or IL-4 was not augmented even when Delta1 (SEQ ID NO:2) was expressed. In addition, cells expressing chimeric receptors hEPO-Delta1R or hMPL-Delta1R did not transduce growth signals in response to EPO

or TPO. To construct the EDER chimeric receptor, a region, which covers the transmembrane domain, and the box1 region of hEPOR was exchanged with the corresponding region of the Delta1. The EDER chimeric receptor responded to hEPO. The experiment demonstrates that a certain region of Delta1 can be swapped into a different receptor but does not disclose any information regarding true ligands or functional characteristics/mechanisms of action of Delta1 receptor. The specification also asserts that the EDER chimeric receptor can activate JAK2. This is not found persuasive because members of the Janus family of protein tyrosine kinases are receptor-associated transducing factors among many cytokine systems including hEPOR. Please see Sharlow *et al.* (1997, Blood, 90:2175-2187) and Zhuang *et al.* (1994, Abstract, Biochemical and Biophysical Research Communications 204:278-283).

The specification asserts several utilities, however the claimed invention lacks specific and substantial utility. A process to screen for receptor agonists and/or antagonists, using probes to isolate other cDNAs with high sequence similarity and making antibodies are not specific utilities. Agonist/antagonist assays are performed for any receptor-ligand pair when the physiological role of each is unknown. Antibodies can be made to any protein. A probe is a general utility that would be applicable to the broad class of the invention. A specific utility is a utility that is specific to the subject matter claimed. This contrasts with a general utility that would be applicable to the broad class of the invention. The specification states that the protein is useful as a tool for screening compounds as drug candidates for immune function related diseases. The specification fails to provide a correlation to the predisposition of a particular disease

and Delta1. Further experimentation is required before this asserted utility is substantial. The utility of a claimed DNA does not necessarily depend on the function of the encoded gene product, if the claimed DNA had a specific and substantial utility such as it hybridizes near a disease-associated gene or it has a gene regulating activity. The specification, however, fails to disclose that the DNA of Delta1 can be linked to a specific disease or has gene regulating activity.

The instant application has failed to provide guidance as to how one of skill in the art could use the claimed invention in a way that constitutes a specific or substantial utility. The proposed uses of the claimed invention are simply starting points for further research and investigation into potential practical uses of the claimed polypeptide.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5 and 7-9 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

The instant invention relates to a novel cytokine receptor-like protein expressed in blood cells. The specification does not teach how to make any variant of the instant invention and provides no reliable assay to evaluate the function of any modified

polypeptide. It is known for proteins as well as nucleic acids, for example, that even a single nucleotide or amino acid change or mutation can destroy the function of the biomolecule in many instances, albeit not in all cases. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Wells, 1990, Biochemistry 29:8509-8517). The specification provides no guidance as to which regions of the cytokine receptor-like protein would be tolerant of modification and which would not, and it provides no working example of any variant sequence which would be within the claims.

The claims are not enabled for a probe with at least 15 bases in length that is specific enough to detect, isolate, purify, enrich or amplify a nucleic acid molecule encoding the cytokine receptor-like protein in a sample with no stringency conditions. In the absence of a recitation of clear hybridization conditions, the instant probe carries the risk of obtaining false signals from unrelated DNA sequences. The instant specification indicates that the polynucleotides are useful in that they encode a protein with a particular activity.

The claims are not enabled for partial peptides. There is no assurance that the partial peptide would have the desirable properties of the instant invention.

The effects of these changes are largely unpredictable as to which ones have a significant effect versus not. The recitation of variants results in an unpredictable and

therefore unreliable correspondence between the claimed biomolecule and the indicated similar biomolecule of known function. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. Without sufficient guidance, the changes which can be made in the structure and still maintain sufficient activity is unpredictable and the experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue.

Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claims 1, 4, 7 and 8 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The specification provides adequate written description for SEQ ID Nos 1 and 2, but not variants. The instant claims are directed to polynucleotides encoding polypeptides set forth in SEQ ID

NO:2 or variants or derivatives thereof, polypeptides comprising the amino acid sequence set forth in SEQ ID NO:2 or variants or derivatives thereof, partial peptides and DNA hybridizing to DNA consisting of the base sequence described in SEQ ID NO:1 with no stringency conditions.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116).

With the exception of SEQ ID Nos 1 and 2, the skilled artisan cannot envision the detailed chemical structure of the encompassed polypeptides and polynucleotides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. In the absence of a recitation of clear hybridization conditions, the nucleic acid probe will hybridize with unrelated DNA sequences, corresponding sequences from other species, mutated sequences, allelic variants, splice variants and so forth. None of these sequences meet the written description provision of 35 USC 112, first paragraph. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See Fiers v. Revel, 25 USPQ2d 1601 at 1606 (CAFC 1993) and Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481 at 1483. In Fiddes, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only isolated polypeptides comprising the amino acid sequence set forth in SEQ ID NO:2 and the polynucleotides comprising the nucleic acid sequence set forth in SEQ ID NO:1, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 4, 7 and 8 rejected under 35 U.S.C. 102(b) as being anticipated by Noguchi *et al.* (Blood 78:2548-2556, 1991, IDS A7, Paper No. 9). The instant claims are generally drawn to DNA hybridizing to the DNA consisting of the base sequence described in SEQ ID NO:1 and encoding a protein that is a functional equivalent of the protein consisting of the amino acid sequence described in SEQ ID NO:2, protein encoded by the DNA thereof, partial peptide of the protein thereof and nucleotide that

hybridizes with the DNA consisting of the base sequence described in SEQ ID NO:1, or the complementary strand thereof, having a chain length of at least 15 bases in length.

In the absence of a recitation of clear hybridization conditions, any polynucleotide sequence will hybridize to SEQ ID NO:1. Noguchi teaches the human erythropoietin receptor (hEPOR) polynucleotide, polypeptide (material and methods, pages 2548-2549, 2550, and 2551. Furthermore, human EPOR also activates JAK2 (functional equivalent of SEQ ID NO:2).

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Regina M. DeBerry whose telephone number is (703) 305-6915. The examiner can normally be reached on Mondays-Fridays 8:00 a.m. - 4:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (703) 308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

RMD
February 21, 2003